Holoprosencephaly: New Concepts

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Since the introduction of the term "arhinencephaly" by Hans Kundrat (1882), investigators have attempted to characterize and further understand the broad spectrum of malformations resulting from a lack of separation of the structures of the forebrain. These malformations are generally lumped under the term "holoprosencephaly" (HPE) coined by DeMyer and Zeman in 1963. These authors further subdivided HPE into the classifications of alobar, semilobar and lobar. More recent work has described a form of HPE in which the basal forebrain is relatively spared and the posterior portion of the frontal lobe is non-cleaved, the middle interhemispheric variant.

While there has been a vast amount of attention in the literature devoted to the complex facial malformations that often accompany the brain parenchymal abnormalities in HPE, it is the generally profound brain anomalies that dominate the clinical picture and prognosis. While the "face predicts the brain" in approximately 80% of cases, it is the brain that predicts the outcome in all. Expanding our knowledge of the extensive brain malformations will allow us to better serve these patients and their families.

Recent discoveries in the fields of genetics and developmental neurobiology have also advanced our knowledge of HPE. The first descriptions of mutations in the gene Sonic hedgehog (Shh) as a causative agent in HPE have given way to the identification and implication of many other gene mutations in the formation of this complex spectrum of disorders. Great strides have been made in understanding human central nervous system development from extrapolating information obtained in cellular fate maps of several animal species. By combining this basic science knowledge with our observations of the brain morphology from imaging studies of a large patient cohort, we can begin to better understand the factors that contribute to the formation of this fascinating spectrum of forebrain malformation. We present evidence that an imbalance of dorsal and ventral patterning signals in the secondary prosencephalon and floor plate result in many of the morphological abnormalities seen in the more common forms of HPE. Ultimately, we hope to further correlate the morphology and biology with neurodevelopmental information, in order to establish more accurate classification of the spectrum and stratification measures for prediction of patient outcome.

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